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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,077	07/09/2004	Roland Kellner	MERCK-2907	3266

23599 7590 01/31/2007

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EXAMINER	
MARTIN, PAUL C	
ART UNIT	**PAPER NUMBER**
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,077	KELLNER ET AL.	
	Examiner	Art Unit	
	Paul C. Martin	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☒ Claim(s) *10* is/are allowed.

6)☒ Claim(s) *1-5,8,9 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 are pending in this application, Claims 6 and 7 are withdrawn as being drawn to non-elected inventions. Claims 1-5 and 8-16 were examined on their merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 1-5 and 8-16 under 35 U.S.C. 112, 1st paragraph as not being enabled for the full scope of the claimed invention has been withdrawn. Applicant's arguments with respect to claims 1-5 and 8-10 have been considered but are moot in view of the new ground(s) of rejection below:

Claims 1-3, 5, 8, 9 and 11-16 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification defines a protein phosphoamidase specific for hydrolyzing N-phosphorylated histidine residues in peptides or proteins having no activity that hydrolyzes O-phosphorylated peptides or proteins exemplified by PHP1 (Specification, Pg. 3, Lines 9-12).

The instant specification further defines a phosphoamidase as an enzyme hydrolyzing phosphoamide (P-N) bonds of phosphorylated basic proteins like P-his, P-Lys, P-Arg, or of peptides or proteins comprising these phosphorylated amino acids and which is devoid of an activity that hydrolyzes O-phosphorylated proteins or peptides, exemplified by the phosphoamidase of Hiraishi *et al.* (1999) and PHP1 (WO/ 0052175) (Specification, Pg. 3, Lines 19-26).

The instant specification further defines a protein phosphoamidase as a phosphoamidase hydrolyzing phosphoamide (P-N) bonds of phosphorylated basic proteins like P-his, P-Lys, P-Arg, or of peptides or proteins comprising these phosphorylated amino acids and which is devoid of an activity that hydrolyzes O-phosphorylated proteins or peptides, exemplified by PHP1 (Specification, Pg. 3, Lines 28-34).

The instant specification again defines a protein histidine phosphoamidase as a protein phosphoamidase specific for hydrolyzing phosphorylated histidine (P-N) within peptides or proteins, as exemplified by PHP1 (Pg. 4, Lines 5-8).

As the Prior Art has repeatedly taught in the instant specification that phosphoamidase, protein phosphoamidase and protein histidine phosphoamidases (including PHP1) will only hydrolyze phosphoamidate (P-N) bonds and is devoid of the activity of hydrolyzing phosphoester (P-O) bonds, the claimed invention is not deemed to be enabled such that enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly since the invention's method for detection, characterization, and qualitative determination of the activity of a phosphoamidase relies upon the hydrolysis of substrates all containing phosphoester (P-O) bonds.

However, it is noted in the instant examples and disclosure that the phosphoamidase PHP1 did unexpectedly hydrolyze certain (P-O) bonded substrates (Specification, Pg. 11, Lines 1-13 and Fig. 7 and 8) an unexpected result over the Prior Art. Therefore, while the instantly claimed invention is not deemed to be enabled such that one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the detection, characterization and qualitative and/or quantitative determination of any phosphoamidase, protein phosphoamidase or protein histidine phosphoamidase by hydrolysis of the claimed phosphoester substrates, the invention is enabled for the detection, characterization and qualitative and/or quantitative determination of PHP1 by hydrolysis of the claimed phosphoester substrates.

Claims 1-3, 5, 8, 9 and 11-16 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim.

In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic.

In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention*. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

In the instant case, the claims are drawn to a method for the identification, characterization, qualitative and/or quantitative determination of the activity of a phosphoamidase/ protein phosphoamidase/ protein histidine phosphatase (PHP1) and the use therein in a method for the identification of inhibitors or activators of a phosphoamidase.

(1) Level of skill and knowledge in the art:

The state of the art indicates that true phosphoamidases are enzymes that hydrolyze the nitrogen phosphorus bond (P-N) of given N-phosphorylated compounds and are free from the activity that hydrolyzes O-phosphorylated compounds (Hiraishi *et al.* (1999), Pg. 368, Column 1, Lines 1-3, 22-24 and Column 2, Lines 1-4) and Ek *et al.* (2002) which taught that PHP1 only hydrolyzed a phosphoamidate phosphorylated peptide and none of a series of phosphoester phosphorylated peptides (Pg. 5020, Lines 19-26).

(2) Partial structure:

The structure of the exemplary phosphoamidase PHP1 is known in and described in the art (see Ek *et al.* (2002).

(3) Physical and/or chemical properties:

As stated above, the properties of phosphoamidases were well known in the art at the time of the instant invention, i.e., the specific hydrolysis of phosphoamidate bonds.

(4) Functional characteristics:

See above.

(5) Method of making the claimed invention:

The method of making the invention calls for the detection of phosphoamidase/ protein phosphoamidase/ protein histidine phosphoamidase through the hydrolysis of substrates containing phosphoester (P-O) bonds.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad genus. Claims 1 and 5 are broadly generic to all possible phosphoamidases encompassed by the claims. The possible variations are enormous to any class of enzymes [EC 3.9.1.1]. Since the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163.

Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of a phosphoamidase which can hydrolyze phosphoester bonds beyond the single example disclosed in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of phosphoamidases possessing phosphoesterase activity.

While having written description of the single phosphoamidase with phosphoesterase activity (PHP1) as identified in the specification and examples, the specification is devoid of any other phosphoamidases that qualify for the functional characteristics claimed.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 11, 13 and 15 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 seems to be missing a detection step wherein the signal derived from the enzymatic hydrolysis of the substrates is detected. Claims 2-4, 13 and 15 are rejected as being dependent upon rejected Claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 8, 9 and 11-16 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Mountfort *et al.* (1999) as evidenced by Kim *et al.* (1993).

In light of the teachings of the Specification and the prior art, the Examiner has deemed that that assay detection method of the instant invention is not enabled for the detection of phosphoamidase. The detection of protein phosphatases and protein phosphatases with phosphoamidase activity however, is possible in the instantly claimed invention.

Mountfort *et al.* teaches the use of the substrate FDP (fluorescein diphosphate) for the detection and quantitative determination of the activity of a protein histidine phosphatase 2a (Pg. 914, Table 1).

Mountfort *et al.* teaches a method for the identification of an inhibitor of a phosphatase comprising:

a) establishing a sample comprising a phosphoamidase and a test substance,

b) administering the substrate FDP to the sample in a buffer based liquid phase,

c) detecting the signal produced by the substrate,

d) Identifying the test substance as an inhibitor of the phosphatase by comparing the signal produced in the sample containing the test substance with the signal produced in a control sample with no test substance (Pg. 911, Lines 20-29 and Pg. 912, Lines 1-3 and Pg.914, Table 1 and Pg. 915, Fig. 2).

Kim *et al.* teaches that protein histidine phosphatase 2a has phosphoamidase activity (Pg. 18514, Column 2, Lines 53-55) and that no published data existed on protein histidine phosphatases, i.e, whether known protein phosphatases that act on phosphoester (P-O) bonds such as phosphoserine, phosphothreonine and phosphotyrosine are also capable of acting on phosphohistidine a phosphoamide (P-N) bond.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of Claims 1-5 and 8-10 under 35 U.S.C. 103(a) as being unpatentable over Hiraishi *et al.* (1999) in view of Mountfort *et al.* (1999) and IUBMB Database [EC 3.9.1.1] (1961) has been withdrawn because the Applicants arguments regarding the phosphoamidase of Hiraishi *et al.* were found to be persuasive. However, upon further consideration new grounds of rejection were made in view of Mountfort *et al.* above.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin
Examiner
Art Unit 1657

01/20/07

JON WEBER
SUPERVISORY PATENT EXAMINER